UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

COPY

NOV 5 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Registration of Mosquito Cognito™ (EPA Symbol. No. 070909-E) containing 95.54% Linalool (Chemical No.128838) as its active ingredient. Review of Product Chemistry, Toxicity, and Efficacy Data (Submission No. S546192; Case No. 063209), MRID Nos. 444458-01, -02, and -03, and 445974-02; DP Barcode D248034.

FROM: Russell S. Jones, Ph.D., Biologist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

THRU: Freshteh Toghrol, Ph.D., Senior Scientist
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

TO: Rita Kumar, Ph.D., Regulatory Action Leader
Biochemical Pesticides Branch
Biopesticides & Pollution Prevention Division (7511C)

ACTION REQUESTED

On behalf of Biosensory Insect Control Corporation, Biologic Inc. requests registration of an end-use product, Mosquito Cognito™ (EPA Symbol. No. 070909-E) containing 95.54% Linalool (Chemical No.128838) as its active ingredient. The registrant also requests waivers from the data requirements for a preliminary analysis study (151-13) and non-target organism/ecotoxicity studies (154-6 to 154-11). In support of the registration, the registrant has submitted product chemistry studies, toxicology data from open literature sources, and efficacy data (MRIDs 449787-01, -02, and -03), and a Confidential Statement of Formula (CSF; dated 12/1/97) for the basic formulation. A rationale for each waiver request was also presented.

CONCLUSIONS AND RECOMMENDATIONS

1. BPB does not support the registration of Mosquito Cognito™ because of deficiencies in the product chemistry and efficacy studies.

2. The data submitted for product identity (151-10), manufacturing process (151-11), certified limits (151-15), and physical/chemical properties (151-17) for the end-use product are acceptable. No additional data are required.

3. A description of the manufacturing process (151-11) for te TGAI/MP is required. Thedescription of the manufacturing process may be provided by either the registrant or the supplier of the TGAI/MP.

4. The discussion of the formation of unintentional ingredients (151-12) for the end-use product was unacceptable, but upgradeable. To upgrade the study, the registration must provide a discussion regarding the nature of the linalool impurity that comprises [redacted] of the end-use product by weight. All reasonable efforts should be made to identify this impurity. Information regarding the linalool impurity may be provided by either the registrant or the supplier of the TGAI/MP.

5. No data were submitted for preliminary analysis (151-13) of the end-use product and a waiver from this data requirement is not granted. The TGAI/MP for the active ingredient [redacted] linalool) is not an EPA registered product and, therefore, preliminary analysis data are required. Since the end-use product is a pheromone formulation (non-food use), the registrant may satisfy this data requirement by submitting any preliminary analysis data that are available, including representative chromatograms.

6. The description of the analytical methods (151-16) is unacceptable, but upgradeable. To upgrade the study, the registrant must submit data pertaining to limits of detection, precision, and accuracy of the method, and representative chromatograms.

7. The registrant must submit a revised CSF. In addition to the correct trade names and CAS numbers, the revised CSF must list the commonly accepted chemical names for each active and inert ingredient in the basic formulation. The CAS number of one of the inert ingredients must be verified.

8. No additional data are required for acute mammalian toxicity (152-10 to 152-15); the active and inert ingredients are not sensitizing agents. The active ingredient and one of the inerts were shown to be non-mutagens (152-17). The active ingredient did not cause toxicity in a 90-day feeding study (152-20). However, the registrant must submit a revised label that contains appropriate precautionary statements and first aid statements (see Label Review below).

9. No additional data are required for non-target organism/ecological effects (154-6 to 154-11). Waivers from the data requirements for these guidelines are granted.

10. The submitted efficacy studies are unacceptable. None of the submitted efficacy data support any of the product label claims nor were they conducted according to Subdivision

M Guidelines 95-9. The registrant must submit new efficacy studies or, in lieu of new studies, the registrant must revise the product label to remove inaccurate efficacy claims (see Label Review below).

STUDY SUMMARIES

Product Chemistry

Product chemistry data (Subdivision M Guidelines 151-10 through 151-17 were presented for Mosquito Cognito™ (MRID 44445801). The end-use product consists of one basic formulation. The active ingredient is linalool (3, 7-dimethyl-1, 6 octadien-3-ol), which comprises 95.54% of the product by weight. The Technical Grade Active Ingredient/Manufacturing-use Product (TGAI/MP) containing the active ingredient, linalool, is not an EPA registered product. The premixed product is purchased from the manufacturer and repacked. A description of the TGAI/MP manufacturing process (151-11) was not submitted. No impurities are likely to be present in the end-use product at ≥0.1% by weight, except for the unspecified linalool impurity. The nature and identity of the linalool impurity were not described. No preliminary analysis data were submitted; these data are required. Acceptable certified ingredient limits (by % weight) were reported by the registrant. An acceptable GC/FID method for the determination of the active ingredient in the end-use product was presented. However, no information regarding precision, accuracy, and limits of detection for the method were reported; these data are required. The data submitted for physical/chemical properties were satisfactory. The CSF was not acceptable and must be revised (see Conclusion 6 above).

Study deficiencies: (i) a description of the manufacturing process for the TGAI/MP was not provided; (ii) the nature and identity of the linalool impurity were not described; (iii) no preliminary analysis data were submitted; (iv) precision, accuracy, and limits of detection data for the analytical method were not reported; (v) and the CSF did not contain the commonly accepted chemical names/and or common names for each active and inert ingredient; additionally, the CAS number for one of the inert ingredients could not be verified.

Classification: Unacceptable, but upgradeable. To upgrade the study, the registrant must resolve the product chemistry deficiencies described above.

Toxicology (MRID 44597401)

No mammalian acute toxicity or irritation studies were submitted. In lieu of toxicity studies, the registrant submitted a compilation of toxicity data/information obtained from open literature sources and study summaries (see Summary of Toxicology and Assessment of Risk; MRID 44597401) in support of acute toxicity, subchronic oral toxicity, genotoxicty, and pharmacokinetics data requirements for the active ingredient. The data used for establishing toxicological categories are summarized in the following table:

Guideline (No.)	Linalool Toxicity Data*	Test Subjects	Tox Category*
Acute Oral (152-10)	LD_{50} = 2790 mg/kg (p. 9).	Rats	III
Acute Dermal (152-11)	LD_{50} = 5610 mg/kg (p. 10).	Rabbits	IV
Acute Inhalation (152-12)	No mortality with 5% solution for unspecified exposure period (p. 10).	Cats	Cannot be assigned but inhalation is not a likely route of human exposure
Primary Eye Irritation (152-13)	Irritation symptoms following 0.1 mL dose; symptoms cleared by day 7 (p. 11).	New Zealand rabbits	III
Primary Dermal Irritation (152-14)	15 dermal irritation studies using a variety of doses were reported; symptoms ranged from no effects to moderate irritation (p. 12).	Rats, rabbits, Guinea pigs, and humans	IV**
Hypersensitivity (152-15)	25 dermal sensitization studies using a wide variety of procedures that are generally recognized as being able to detect skin sensitization (p. 13).	Primarily humans (with three Guinea pig studies)	Not a sensitizing agent based on the negative results observed in most of the human studies.
90-Day Subchronic Oral Toxicity Study (152-20)	Oral dose of 500 mg/kg linalool for 64 days. Other than an unspecified increase in liver weights, no toxicity effects were observed (p. 14).	Four male rats	NOEL >500 mg/kg
Genotoxicity (152-17)	Negative results were reported for five Ames Assay studies and an "Unscheduled DNA Synthesis" study; a mouse lymphoma study gave weakly positive results in cells induced with S9 (p. 16).	*S. typhimurium and E. coli*; Fischer and Sprague-Dawley rats; and L5178Y TK+/- cells, respectively	Not a mutagen
Pharmacokinetics (OPPTS 870.8223)	Feeding studies with radiolabelled linalool indicated that 55% of the dose was excreted in the urine, 15% in the feces, and 23% was respired into the air. Dihydro and tetrahydrolinalool were identified in the urine. Metabolites in feces and the bile duct were not identified but were reported to be comprised of mainly polar, ether-soluble conjugates.	two Wistar rats	Not applicable

* Only those studies used to establish toxicity categories were used in the table above. Data from other study summaries submitted by the registrant in (MRID 44597401) were reviewed, but not reported here.

** Based on a study (Moreno et al., 1980), showing that slight dermal irritation symptoms on rats cleared after three to six weeks of continuous dosing with linalool at 250 mg/kg and 1.00 g/kg, respectively.

The registrant also submitted summaries of acute toxicity studies from the open literature for each of the inert ingredients. The data from these studies indicate that the inerts would be classified in Tox category III and/or IV for acute oral toxicity, acute dermal toxicity, primary eye irritation, and/or primary dermal irritation. Summarized toxicity studies for the inert ingredients are included in the Confidential Appendix of this document.

Using open literature sources (MRID 44597401), the registrant showed that linalool was approved by FDA as a direct food additive and was given Generally Recognized As Safe (GRAS) status for use as a flavor in both human and animal food under the following FDA regulations: (i) 21 CFR 172.515, Food Additives Permitted for Direct Addition to Food for Human Consumption; (ii) 21 CFR 182.60, Substances Generally Recognized As Safe, Food for Human Consumption Synthetic Flavoring Substances and Adjuvants; (iii) and 21 CFR 582.60, Substances Generally Recognized as Safe, Animal Drugs, Feeds, and Related Products The GRAS status for linalool use in human food was approved in 1965 (p. 8). The Council of Europe (1974) and the Joint FAO/WHO Expert Committee also gave linalool an acceptable daily intake of up to 0.25 mg/kg. The active ingredient is used in many consumer products including soaps, detergents, and perfumes with concentrations in products varying from 0.03 to 1.5% of the final product. Additional information were presented by the registrant showing that if humans were to consume an entire 15 g dispenser of product, the ingested linalool would be equivalent to 716 mg/kg for a 20 kg child, 205 mg/kg for a 70 kg adult male, and 358 mg/kg for an adult female (p. 18). These values are far below the acute oral LD_{50} (2790 mg/kg) for linalool. The registrant also showed that if humans were dermally exposed to 100% of the amount of linalool that is released daily by the product dispenser (4.75 mg), the maximum absorbed would be equivalent to 47.5 mg/kg for a 10 kg child, 6.8 mg/kg for a 70 kg adult male, and 11.9 mg/kg for an adult female (p. 18). These values are far below the acute dermal LD_{50} (5610 mg/kg) for linalool. Similar oral and dermal exposure data were calculated for each of the inert ingredients in the end-use product. The maximum theoretical oral and dermal exposures for each inert were also well below the respective oral and acute LD_{50}s for each inert.

Classification: Acceptable. Although some of the toxicity studies are considered supplemental because they were not conducted according to guideline requirements, GLPs, and/or many experimental details were lacking. No additional toxicity data are required.

Non-target Organisms and Ecological Effects

No ecological effects or non-target organism studies were submitted. In lieu of these studies, the registrant requested a waiver from the data requirements because there is no direct exposure of the product to birds, fish, aquatic invertebrates, or plants. The product is contained within a screened, electronic killing device. Therefore, effects on non-target insects would be random, incidental, and negligible. No additional data are required.

Efficacy Data

Two field studies were conducted in Florida. The first study (consisting of one trial each in September and October 1996) was conducted to determine the potential of the active ingredient to inhibit the host-seeking ability of mosquitoes. In the September trial, a prototype of the product dispenser was used, whereas in the October trial, target devices treated with the active ingredient were used. Each study showed that the active ingredient (linalool) was partially effective in reducing mosquito activity around traps baited with heat and CO_2 (to simulate a large mammal). However, no data were submitted to support the product label claim that the end-use product can protect up to 10 people. Additionally, the duration of repellency could not be assessed.

The second field study (consisting of three trials conducted on a site adjacent to a wooded wetland in February 1998) was used to determine if linalool can be used as a repellent to reduce mosquito biting activity on humans in outdoor areas with moderate to high mosquito populations. The end-use product was shown to be partially effective in reducing the number of mosquito landings 36% to 68% relative to the number of landings observed in the nontreated control area (Trials 1 and 2). When tested at a time of low mosquito activity (Trial 3), landings were reduced 73%. However, the product did not provide complete protection from mosquitoes and its effectiveness decreased as mosquito landing pressure increased. Additionally, only one human test subject was used; this same test subject was also used for both the treated and control areas. The use of only one human test subject for the entire study seriously comprises the usefulness of the study and does not support product label claims for the protection of up to 10 people.

Classification: Unacceptable. The registrant must submit new efficacy studies to support product label claims. In lieu of additional studies, the registrant must revise the product label (including the label for the replaceable cartridges) to correct inaccurate product performance claims.

LABEL REVIEW

General: The signal word "CAUTION" and the statement "Keep Out of Reach of Children" that are listed on the proposed label are appropriate. The product label does not contain any other precautionary statements or First Aid (Statement of Practical Treatment) statements.

Toxicity: Acute toxicity studies demonstrate that the active ingredient should be classified in Toxicity Category III for acute oral toxicity and primary eye irritation (Subdivision M Guidelines 152-10 and 152-13, respectively). Therefore, the product label must contain a Precautionary Statement and First Aid (Statement of Practical Treatment) statements appropriate for these toxicity categories. Appropriate label statements are attached.

Efficacy: The submitted efficacy studies were unacceptable and did not support any of the product label claims. In lieu of additional efficacy studies, the registrant must revise the label by removing the statement **"...mosquitoes literally cannot detect your presence. If they can't find you, they can't bite you."** The submitted efficacy data (MRIDs 44445803 and 44597402) indicate that mosquitoes can detect product-treated traps baited with heat and CO_2 (simulating a large mammal) and a human walking within a treated area. Additionally, the registrant must remove the statement **"Protects a Party of up to 10 people."** The registrant submitted efficacy data showing that only one human could be *partially* protected mosquitoes over approximately 2-3 hour experimental periods. The registrant should add appropriate language (or a disclaimer) to the product label showing that the product reduces, but does not provide complete protection from mosquito bites and that product effectiveness is dependent upon insect activity in the treated area. Furthermore, the statement **"Last 30 Days"**, should be footnoted to show that the scent of the product lasts 30 days, not necessarily the repellent activity. Additionally, the registrant should add language specifying the number of dispensers that need to be used per unit of surface area (e.g. the number of dispensers per square foot).

Unless the registrant can provide data that support the efficacy claims made on the proposed product label, the above mentioned label revisions must be made.

cc: F. Toghrol, R. S. Jones, R. Kumar, BPPD Subject File
R. S. Jones: F.T. CM2, (703) 308-5071: 11/4/98

ATTACHMENT

Label Precautionary Statements and First Aid (Statement of Practical Treatment) Statements

#: 070909-00002 MOSQUITO COGNITO

SIGNAL WORD: CAUTION

PRECAUTIONARY STATEMENTS:

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet.

STATEMENT OF PRACTICAL TREATMENT (SOPT):

IF SWALLOWED: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger. If person is unconscious, do not give anything by mouth and do not induce vomiting.

OR

IF SWALLOWED: Call a physician or Poison Control Center. Drink 1 or 2 glasses of water and induce vomiting by touching back of throat with finger, or if available by administering syrup of ipecac. If person is unconscious, do not give anything by mouth and do not induce vomiting.

IF IN EYES: Flush eyes with plenty of water. Call a physician if irritation persists.

CONFIDENTIAL APPENDIX

The Following Section Contains Confidential Business Information (CBI)

DATA EVALUATION REPORT

Reviewed by: Russell S. Jones, Ph.D. BPPD
Secondary Reviewer: Freshteh Toghrol, Ph.D. BPPD

STUDY TYPE:	Product Chemistry (Subdivision M Guidelines 151-10 to 151-17)
TOX. CHEM. No.:	526A
CASE No.	063209
PC CODE:	128838
DP BARCODE:	D248034
SUBMISSION No.:	S546192
MRID No:	444458-01
TEST MATERIAL:	Mosquito Cognito™
STUDY No:	Laboratory Project ID: BIO-MOSQ-CHEM
SPONSOR:	Biosensory Insect Control Corporation, 115 Poheganut Drive, Suite 301, Groton, CT 06340
TESTING FACILITY:	Biosensory Insect Control Corporation, 115 Poheganut Drive, Suite 301, Groton, CT 06340
TITLE OF REPORT:	Biosensory Insect Control Corporation, Mosquito Cognito™, Product Chemistry
AUTHOR:	James Nolen
REPORT ISSUED:	December 1, 1997
QUALITY ASSURANCE:	The submitter of the product chemistry study contained in MRID 44445801, indicated that it was not known whether the study was conducted in accordance with Good Laboratory Practices (GLPs). A noncompliance statement was signed by the representative for the registrant, Jane M. Miller (Biologic, Inc.), dated 12/6/97.

SUMMARY: Product chemistry data (Subdivision M Guidelines 151-10 through 151-17 were presented for Mosquito Cognito™ (MRID 44445801). The end-use product consists of one basic formulation. The active ingredient is linalool (3, 7-dimethyl-1, 6 octadien-3-ol), which comprises 95.54% of the product by weight. The TGAI/MP containing the active ingredient, linalool, is not an EPA registered product. The registrant did not provide a description of the manufacturing process for the TGAI/MP; this information is required. In % by weight, the following inert ingredients are present in the basic formulation: an unspecified linalool impurity [redacted] The premixed product (not registered by EPA) is purchased from the manufacturer and repacked. No impurities are likely to be present in the end-use product at ≥0.1% by weight, except for the unspecified linalool impurity. The nature and identity of the linalool impurity were not described. No preliminary analysis data were submitted; these data are required. The following certified ingredient limits (by % weight) were reported by the registrant: Linalool [redacted] An acceptable GC/FID method for the determination of the active ingredient in the end-use product was presented. However, no information regarding precision, accuracy, and limits of detection for the method were reported. The end-use product is a colorless liquid with a mild floral odor. It has a specific gravity of approximately 0.86 g/mL at 25°C and a boiling point of approximately 198°C. The product is soluble in water (0.78M at 25°C). It does not contain oxidizing or reducing agents, is not potentially explosive, is stable under normal use conditions, and stable under normal storage conditions for a minimum of one year. The product has a flash point of >230°C.

CLASSIFICATION: Unacceptable, but upgradeable. To upgrade the study, the registrant provide the following information/data: (i) a description of the manufacturing process for the TGAI/MP for linalool; (ii) a discussion pertaining to the nature of the linalool impurity that comprises [redacted] of the end-use product by weight; (iii) preliminary analysis data for the end-use product; (iv) data pertaining to precision, accuracy, and limits of detection for the analytical method; these data should be accompanied by representative chromatograms; (v) a revised CSF that lists the complete chemical name for the active ingredient, linalool (3, 7-dimethyl-1, 6-octadien-3-ol) and the inert ingredients [redacted] the Agency cannot verify the accuracy of this number.

Product ingredient source information may be entitled to confidential treatment

Manufacturing process information may be entitled to confidential treatment

Inert ingredient information may be entitled to confidential treatment

I. PRODUCT IDENTITY AND DISCLOSURE OF INGREDIENTS (151-10)

A. Linalool (3,7-dimethyl-1,6-octadien-3-ol)

Ingredient: Active
CAS Number: 78-70-6
Empirical Formula: C10 H18 O
Chemical Characterization: Mosquito pheromone
Supplier: [redacted]

Contains: Linalool impurity (unspecified)

[redacted]

Inert ingredient information may be entitled to confidential treatment

Product ingredient source information may be entitled to confidential treatment

[redacted]

II. MANUFACTURING PROCESS (151-11)

[redacted]

Manufacturing process information may be entitled to confidential treatment

III. DISCUSSION OF THE FORMATION OF IMPURITIES (151-12)

[redacted]

[redacted]

IV. PRELIMINARY ANALYSIS (151-13)

[redacted]

V. CERTIFICATION OF INGREDIENTS (151-15)

The nominal concentrations and certified ingredient limits (by % weight) were as follows:

[redacted]

VI. ENFORCEMENT ANALYTICAL METHODS (151-16)

[redacted]

VII. PHYSICAL AND CHEMICAL CHARACTERISTICS (151-17)

The physical and chemical properties of the new end-use product were submitted in MRID 44498701.

Property	End-use Product (EP)
Color	Colorless
Physical state	Liquid
Odor	Mild floral
Melting point	Not Applicable (N/A); product is a liquid
Boiling point	Approximately 198°C at 3 mm Hg
Specific gravity	Approximately 0.86 g/mL at 25°C
Solubility	0.78 M in water at 25°C
Vapor pressure	6.32×10^{-8} mm Hg at 25°C
Dissociation constant	N/A; does not dissociate
Octanol/water partition coefficient	$K_{ow} = 68$
pH	Not required (NR); not dispersable in water
Oxidation/reduction potential	NR; does not contain oxidizing/reducing agents
Explodability	NR; not potentially explosive
Stability	Stable under normal use conditions
Flammability	Flashpoint >230°F
Storage stability	Stable for a minimum of 1 year under normal use conditions
Viscosity	NA
Miscibility	NR; not emulsifiable and not diluted with petroleum solvents
Corrosion characteristics	Not corrosive
Dielectric breakdown voltage	NR; not for use around electrical equipment

DISCUSSION

The product identity and disclosure of ingredients were adequately described, and the manufacturing process for the end-use product was sufficiently explained. However, the registrant did not provide a description of the manufacturing process for the TGAI/MP

containing the active ingredient, linalool. The TGAI/MP is not an EPA registered product and, therefore, a description of the manufacturing process is required. Discussion of the formation of unintentional ingredients was not satisfactory because the registrant did not adequately describe the nature of the linalool impurity [redacted] of the product by weight). No preliminary analysis data were submitted; these data are required because the TGAI/MP containing the active ingredient is not an EPA registered product. The certified ingredient limits were adequately described. An acceptable GC/FID analytical method was submitted for the determination of the active ingredient in the end-use product. The description of the analytical method was satisfactory, but the registrant did not submit data pertaining to limits of detection, precision, and accuracy, and representative chromatograms were not presented; these data are required. The submitted physical/chemical properties table was satisfactory.

STUDY DEFICIENCIES

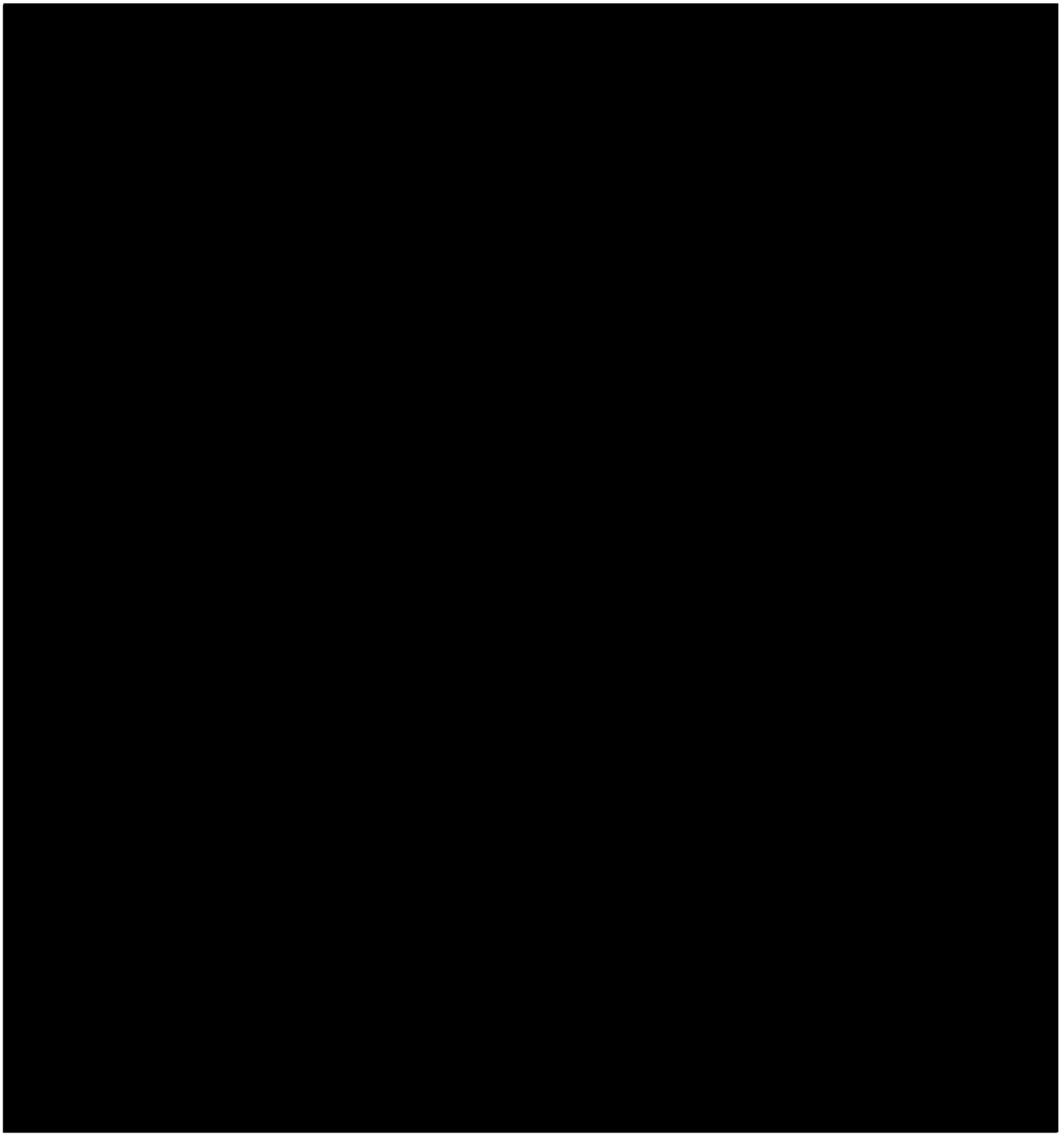
The registrant did not provide a description of the manufacturing process for the TGAI/MP nor adequately describe the nature of the linalool impurity, which comprises [redacted] (by weight) of the end-use product. This information is required. Data pertaining to limits of detection, precision, and accuracy were not submitted for the GC/FID analytical method and representative chromatograms were not presented; these data are required. The chemical names for the active and inert ingredients were not listed on the CSF [redacted]

Manufacturing process information may be entitled to confidential treatment

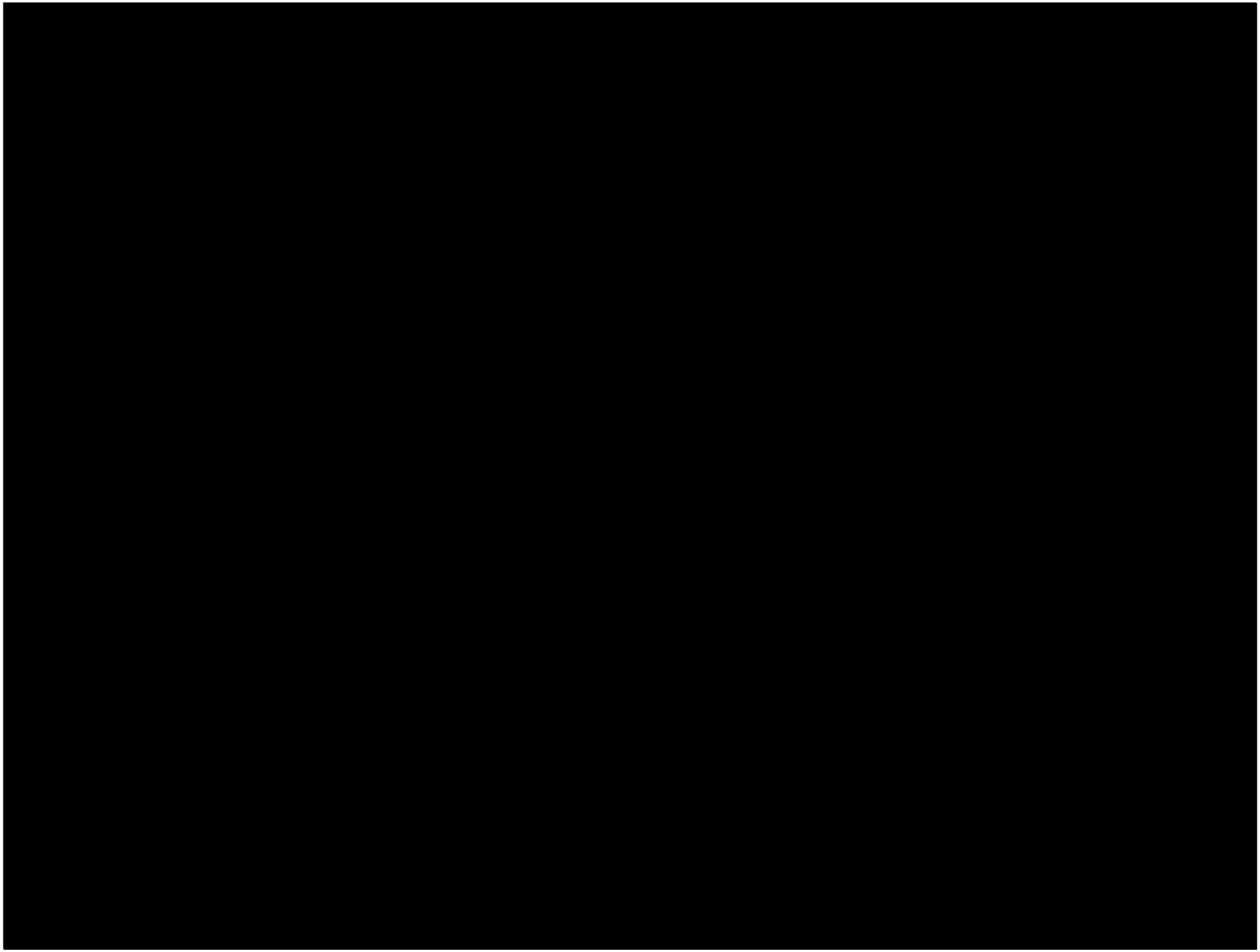
Inert ingredient information may be entitled to confidential treatment

TOXICOLOGY STUDY SUMMARIES: INERTS (MRID 44597401)

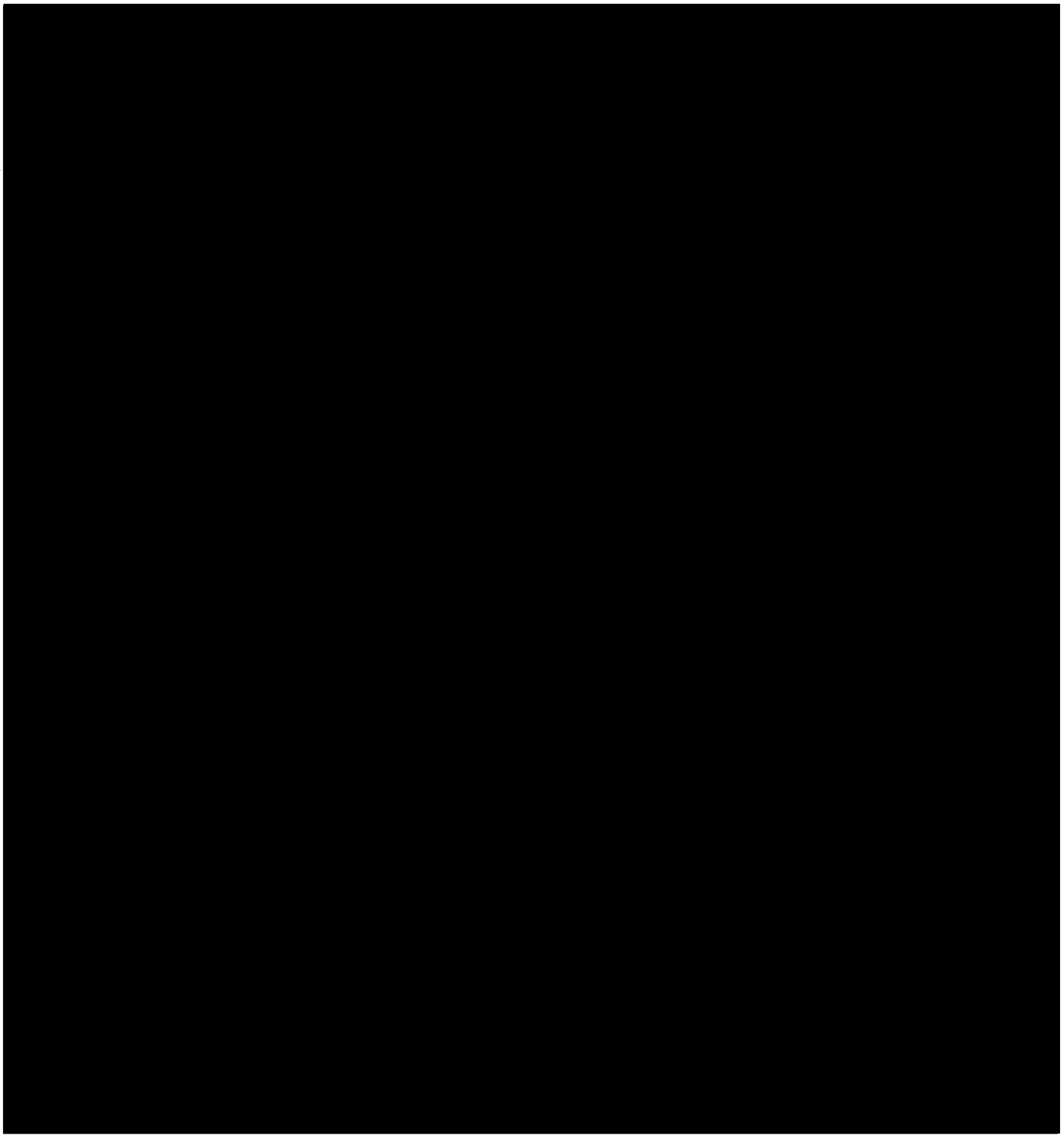
Toxicity data /information (152-10 to 152-15, and 152-17 and 152-20) pertaining to the active ingredient, linalool, are discussed in the non-confidential portion of this document. Acute toxicology data submitted for each of the inert ingredients in MRID 44597401 are summarized below.



Inert ingredient information may be entitled to confidential treatment



Additional Toxicology/Exposure Information for the Inert Ingredients



Inert ingredient information may be entitled to confidential treatment

DATA EVALUATION REPORT

Reviewed by: Russell S. Jones, Ph.D. BPPD
Secondary Reviewer: Freshteh Toghrol, Ph.D. BPPD

STUDY TYPE:	Mosquito Efficacy Studies (Subdivision M Guidelines 95-10)
TOX. CHEM. No.:	526A
CASE No.	063209
PC CODE:	128838
DP BARCODE:	D248034
SUBMISSION No.:	S546192
MRID Nos:	44445803 and 44597402
TEST MATERIAL:	Mosquito Cognito™
STUDY Nos:	BIO-MOSQ-EFF and MC-95
SPONSOR:	Biosensory Insect Control Corporation, 115 Poheganut Drive, Suite 301, Groton, CT 06340
TESTING FACILITY:	USDA, ARS, CMAVE, Gainesville, FL 32608
TITLE OF REPORTS:	Mosquito Cognito™ Studies Conducted at Sarasota, FL (MRID 44445803); and Summary of Field Observations of Linalool as an Inhibitor (MRID 44597402).
AUTHOR:	Daniel L. Kline, Ph.D.
REPORT ISSUED:	December 1, 1997 (MRID 44445803); and February 28, 1998 (MRID 44597402).
QUALITY ASSURANCE:	The submitter of the efficacy study submitted in MRID 44445803 indicated that it was not known whether the study was conducted in accordance with Good Laboratory Practices (GLPs); the efficacy study submitted in MRID 44597402 was not conducted according to GLPs. Noncompliance statements were signed by the representative

for the registrant, Lawrence Miller (Biologic, Inc.), on 12/6/97 and 7/7/98.

SUMMARY:

Two field studies were conducted in Florida. The first study (consisting of one trial each in September and October 1996) was conducted to determine the potential of the active ingredient to inhibit the host-seeking ability of mosquitoes. In the September trial, a prototype of the product dispenser was used, whereas in the October trial, target devices treated with the active ingredient were used. Each study showed that the active ingredient (linalool) was partially effective in reducing mosquito activity around traps baited with heat and CO_2 (used to simulate a large mammal). Octenol further reduced activity around heat and CO_2-baited traps in only one of the two tests. No data were submitted to support the product label claim that the end-use product can protect up to 10 people. Additionally, the duration of repellency could not be assessed.

The second field study (consisting of three trials conducted on a site adjacent to a wooded wetland in February 1998) was used to determine if linalool can be used as a repellent to reduce mosquito biting activity on humans in outdoor areas with moderate to high mosquito populations. The end-use product was shown to be partially effective in reducing the number of mosquito landings 36% to 68% relative to the number of landings observed in the nontreated control area (Trials 1 and 2). When tested at a time of low mosquito activity (Trial 3), landings were reduced 73%. However, the product did not provide complete protection from mosquitoes and its effectiveness decreased as mosquito landing pressure increased. Additionally, the use of only one test subject for both the treated and control areas seriously comprises the usefulness of the study and does not aid in the support of product label claims for the protection of up to 10 people.

CLASSIFICATION:

Unacceptable. The registrant must submit new efficacy studies to support product label claims. In lieu of additional studies, the registrant must revise the product label (including the label for the replaceable cartridges) to correct inaccurate and misleading product performance claims.

I. Study 1. Summary of Field Observations of Linalool as an Inhibitor (MRID 44445803)

Two field studies were conducted, one each in September and October 1996, to determine the potential of the active ingredient to inhibit the host-seeking ability of mosquitoes. Both studies were conducted at the Florida Medical Entomology Research Laboratory, Vero Beach, FL.

A. MATERIALS AND METHODS

September 1996: One "Breadboard" (a working prototype of the product dispenser system) was used. The Breadboard was operated at 110°F with 50 mL/min CO_2 supplied form a compressed gas cylinder. The following treatments were used: (i) heat and CO_2 only; (ii) heat, CO_2 , and octenol (7 mg/hr); (iii) heat, CO_2, and linalool (7 mg/hr); and (iv) heat, CO_2 , octenol (7 mg/hr), and linalool (7 mg/hr). A standard, unlighted CDC trap baited with 500 mL/min of CO_2 was used as a to measure mosquito activity; the CDC was placed at a separate, but constant location approximately 250 feet away from the Breadboard. Since there was only one Breadboard available for testing, treatments were randomly assigned to different days of the week. The location remained the same throughout the field study. There were three reps per treatment. No human subjects were present to test protection from mosquito landing/biting in the field.

October 1996: Heated cylindrical targets (395 in^2 with a 75-watt bulb; IR surface signature of 0.2 watts/in^2) were baited with CO_2 as previously described. Tests were conducted over a two-day period with six targets used per day. On day 1, three targets were baited with heat and CO_2 only, and three targets were baited with heat, CO_2, and one target each with linalool at 7, 14, or 28 mg/hr. On day 2, linalool-treated targets were also treated with octenol (14 mg/hr). A CDC trap (previously described) was used each night of the trial to determine mosquito activity. All treatments were located at least 40 feet apart from each other. No human subjects were present to test protection from mosquito landing/biting in the field.

B. OBSERVATIONS

September 1996: Linalool and linalool plus octenol reduced mosquito collections by 58.8% and 82.8%, respectively, relative to traps baited respectively with heat and CO_2 or heat, CO_2, and octenol. Mosquitoes trapped in the CDC trap fluctuated daily, but no values were reported (see Table 1 below).

October 1996: Linalool and linalool plus octenol reduced mosquito collections by 57.4% (*Aedes taeniorrhyncus*; see MRID 44597402, p. 4) and 45.6% (*Culex nigripalpus*; see MRID 44597402, p. 4), respectively, relative to traps baited respectively with heat and

CO_2 or heat, CO_2, and octenol. There were 220 and 156 mosquitoes trapped in the CDC trap on days 1 and 2 respectively. The study author did not explain how two different species of mosquito were collected from the same traps on two different days (see Table 1).

Table 1. Inhibition of Mosquitoes from Locating Traps Treated with Linalool[1]

Treatment	September 1996		October 1996	
	Mean No. Mosquitoes Collected/Night	% Reduction	Mean No. Mosquitoes Collected/Night	% Reduction
CO_2 + heat	201.3	-	1707.0	-
CO_2 + heat + L[2]	83.0	58.8	727.0	57.4
CO_2 + heat + O[3]	262.0	-	281.7	-
CO_2 + heat + O + L	45.0	82.8	153.3	45.6

1 Data obtained from MRID 44445803, Tables 1 and 2, p. 5.
2 Linalool
3 Octenol

C. CONCLUSIONS

Linalool is partially effective in reducing mosquito activity around traps baited with heat and CO_2. Octenol further reduced activity around heat and CO_2-baited traps in only one of the two tests. No data were submitted to support the product label claim that the end-use product can protect up to 10 people. Additionally the duration of repellency could not be assessed.

D. STUDY DEFICIENCIES

None of the submitted data support any of the product performance claims listed on the proposed product label. The actual end-use product (Mosquito Cognito™) was not used in the October field trials, and it is not known how well the treated targets/traps simulated the activity the end-use product in the field. No raw data were submitted and no statistical analysis was conducted. Mosquito collections for each of the different linalool treatments in the October trials were not reported. Mosquito species collected in the traps were not reported in this study, but were identified in a companion study (MRID 44597402) that referred to these trials. Additionally, two different species of mosquito were collected on two different nights during the October 1996 trial but the study author

did not explain why this occurred. Temperature, humidity, and precipitation during application and during the observation period were not reported.

E. CLASSIFICATION

Unacceptable, due to the deficiencies described above.

II. Study 2. Mosquito Cognito™ Studies Conducted at Sarasota, Florida (MRID 44597402)

One field study was conducted on a site adjacent to a wooded wetland in Sarasota, FL in February 1998. The goal of the study was to determine if linalool can be used as a repellent to reduce mosquito biting activity on humans in outdoor areas with moderate to high mosquito populations, and to reduce conventional pesticide use for that purpose.

A. MATERIALS AND METHODS

Due to the time of year , not all species of mosquito were active and no biting flies were present. After sunset, temperature sometimes fell below 13°C (55°F), the threshold of mosquito activity. A CDC trap baited with 200 mL/min CO_2 (equivalent to a 91-kg or 200 lb adult male) was run continuously each night as a control. The CDC trap indicated that the mosquito population was 91% *C. nigripalpus*. The experimental design was a 2 x 2 Latin Square. Field trials were conducted in two open areas that were 80 feet apart; each area was 8 square feet. On alternate nights, Mosquito Cognito dispensers were placed on wooded stakes located in the corners of one area; the other area was left unprotected. The dispensers released the product (containing 95% a.i.) at a rate of 20 to 40 mg/hr). Efficacy of the product was assessed by measuring the number of landings on the arms, legs, and torso of a human test subject known to be moderately attractive to mosquitoes. The test subject was seated at the center of the square area containing the product dispensers. At 15-minute intervals over a two to three hour period, the same human subject alternated between the treated area and the untreated area. If there was no mosquito activity for five minutes, the researcher walked around the inside perimeter of the square area to draw attention to his presence. Mosquitoes that landed were killed to prevent double counting. Three trials were conducted on three different days: (I) 5:15-7:00 pm on 2/14/98; (ii) 5:15-8:00 pm on 2/18/98; and (iii) 7:00-8:15 am on 2/19/98. Peak mosquito activity was observed to occur at 6:45- 7:00 pm.

B. OBSERVATIONS

The following table (data obtained from MRID 44457402, pp. 7 and 8) shows the percentage of mosquito landings on a human test subject in the treated and untreated areas on three different dates and times.

Trial (time)	Mosquito Landings			% Landing in Treated Area	% Landing Reduction by Treatment
	CDC Control	Nontreated Control	Treatment		
1 (5:15-7:00 pm)*	80	130	41	32	68
2 (5:15-8:00 pm)*	277	141	90	64	36
3 (7:00-8:15 am)	Not Used	15	4	27	73

* Peak mosquito activity was at 6:45-7:00 pm.

C. CONCLUSIONS

The end-use product was partially effective in reducing the number of mosquito landings. During testing periods that spanned the times of peak mosquito activity (Trials 1 and 2), landings on a human subject were reduced 36% to 68% relative to the number of landings observed in the nontreated control area. When tested at a time of low mosquito activity (Trial 3), landings were reduced 73%. The product does not provide complete protection from mosquitoes and its effectiveness decreased as mosquito landing pressure increased. Additionally, the use of only one test subject for both the treated and control areas seriously comprises the usefulness of the study and does not aid in the support of product label claims for the protection of up to 10 people.

D. STUDY DEFICIENCIES

Only one test subject was used, precluding any statistical analysis. None of the submitted data support any of the product performance claims listed on the proposed product label. No raw data were submitted and no statistical analysis was conducted. Mosquito species collected in the traps were not reported in this study, but were identified in a companion study (MRID 44597402) that referred to these trials. Additionally, two different species of mosquito were collected on two different nights during the October 1996 trial but the study author did not explain why this occurred. Temperature, humidity, and precipitation during application and during the observation period were not reported.

E. CLASSIFICATION

Unacceptable for the reasons given in the deficiencies above.